BRIEF COMMUNICATION

Insulin Resistance and Prostate Cancer Risk

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Because high waist-to-hip ratio (WHR) and high serum insulin levels have been reported to be associated with an increased risk of prostate cancer, we assessed the relationship between insulin resistance and prostate cancer risk in Chinese men. We measured fasting serum glucose and insulin levels in 128 case and 306 control subjects and used the homeostasis model assessment to derive indices of insulin sensitivity and resistance. Relative to men in the lowest tertiles, men in the highest tertile of insulin sensitivity had a reduced risk of prostate cancer (odds ratio [OR] = 0.35, 95% confidence interval [CI] = 0.21 to 0.60), but men in the highest tertile of insulin resistance had an increased risk of prostate cancer (OR = 2.78, 95% CI = 1.63 to 4.72). Considering insulin resistance and WHR together, the effect of insulin resistance was apparent in all tertiles of WHR, with men in the highest tertile of insulin resistance and WHR having the highest risk (OR = 8.21, 95% CI = 2.84 to 23.70). The associations between prostate cancer risk and insulin sensitivity or resistance were independent of total caloric intake and serum levels of insulin-like growth factors, sex hormones, and sex hormone-binding globulin. Because of the retrospective design of this study, the role of insulin resistance in prostate cancer needs to be confirmed in prospective studies. [J Natl Cancer Inst 2003;95:67–71]

Chinese men have an average body mass index (BMI) that is considerably lower than the average BMI of Western populations *(1).* We previously reported that high waist-to-hip ratio (WHR) and high serum insulin levels were associated with a statistically significant excess risk of prostate cancer among Chinese men *(1,2).* The insulin–prostate cancer association was independent of BMI and WHR and independent of serum levels of insulin-like growth factor I (IGF-I), sex hormones, and sex hormone-binding globulin (SHBG) *(1).* Because high insulin levels can be associated with insulin resistance (i.e., the reduced sensitivity of tissues to the action of insulin), we sought to determine the relationship between insulin resistance and risk of prostate cancer.

We tested the hypothesis that insulin resistance is associated with prostate cancer risk by using a population-based case–control study conducted in Shanghai from 1993 through 1995. Details of the study design and population have been reported elsewhere *(1–5).* For this study, subjects who had sufficient fasting sera for various assays were selected, including a total of 128 case subjects and 306 population control subjects. Only case subjects whose blood samples were collected before treatment were included in this study.

We measured fasting levels of serum glucose (G_0) and insulin (I_0) and derived indices of insulin sensitivity and insulin resistance. Insulin sensitivity (IS) was measured by the homeostasis model assessment [HOMA-IS $= 10\,000/(I_0 \times G_0)$] *(6)* and the quantitative insulin sensitivity check index *(7)* {QUICKI index: 1/[log (fasting insulin μU/mL) + log (fasting glucose mg/dL)]}. Insulin resistance (IR) was measured by the ratio of insulin to glucose (I_0/G_0) and the HOMA-IR index [HOMA-IR = fasting insulin (μU/mL) × glucose (mmol/L)/ 2 2 . 5] .

The HOMA β-cell function [(HOMA-β) $= (20 \times I_0)/(G_0 - 3.5)$], which measures pancreatic β-cell function, was also assessed *(6).* Fasting serum insulin and glucose were measured by commercially available radioimmunoassay kits (Linco Research, St. Charles, MO) in the laboratory of Dr. F. Z. Stanczyk. The sensitivity limits for the insulin and glucose assays were 2 μU/mL and 0.5 ng/mL, respectively, and the intra- and interassay coefficients of variation were 4.0% and 6.0%, respectively, for the insulin assay and 3.0% and 4.9%, respectively, for the glucose assay. Plasma levels of IGF-I and IGF-II and the binding proteins (IGFBP-1 and IGFBP-3) were assayed by Diagnostic Systems Laboratory (Webster, TX), and testosterone (T), dihydrotestosterone (DHT), and 5α-androstane-3α, 17β-diol glucuronide (3α-diol G) were measured by radioimmunoassay in the laboratory of Dr. F. Z. Stanczyk *(8).* Written informed consent was obtained from each study subject, and the study was approved by the Institution Review Boards at the National Cancer Institute (Bethesda, MD) and the Shanghai Cancer Institute.

In the analysis, we used two indices of insulin resistance to demonstrate that any association between insulin resistance and prostate cancer risk is independent of the tool chosen to quantify insulin resistance. Insulin resistance occurs when a normal concentration of insulin produces a less than normal biologic response. The euglycemic insulin clamp *(9)* is the gold standard method of assessing insulin resistance because it provides steady-state measures of insulin action. However, it is a labor-intensive procedure that is useful primarily for physiologic studies with small numbers of subjects *(9).* The HOMA and QUICKI indices are quantitative estimates of insulin sensitivity and resistance useful for population studies *(9–11).* In two validation studies *(9,10),* these indices correlated well with results from the euglycemic insulin clamp technique.

Selected characteristics were compared between case and control subjects with *P* values derived from *t* tests and Mantel–Haenszel chi-square tests. Log-transformation of insulin-related indices was performed, whenever necessary, to meet the normality assumption. Possible correlations of selected factors with insulin resistance among control subjects

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See "Notes" following "References."

Table 1. Spearman correlation coefficients between selected variables associated with insulin sensitivity and insulin resistance among 306 male population control subjects from Shanghai, China*

	Insulin	Glucose	HOMA insulin sensitivity†‡	QUICKI insulin sensitivity‡	I_0/G_0 ratio	HOMA I/G ratio	HOMA β-cell function‡
Insulin	1.0						
Glucose	0.09 $P = .10$	1.0					
HOMA insulin sensitivity	–0.87 $P<.001$	–0.51 $P<.001$	1.0				
QUICKI insulin sensitivity	–0.87 $P<.001$	–0.51 $P<.001$	1.0 $P<.001$	1.0			
Insulin resistance I_0/G_0 ratio	0.86 $P<.001$	–0.34 $P<.001$	–0.54 $P<.001$	–0.54 $P<.001$	1.0		
HOMA I_0/G_0 ratio	0.87 $P<.001$	0.51 $P<.001$	–1.00 $P<.001$	–1.00 $P<.001$	0.54 $P<.001$	1.0	
β-cell function	0.85 $P<.001$	–0.35 $P<.001$	–0.53 $P<.001$	–0.53 $P<.001$	1.0 $P<.001$	0.53 $P<.001$	1.0
Body mass index	0.28 $P<.001$	0.02 $P = .69$	–0.24 $P<.001$	–0.24 $P<.001$	0.27 $P<.001$	0.24 $P<.001$	0.27 $P<.001$
Waist circumference	0.42 $P<.001$	0.02 $P = .73$	–0.37 $P<.001$	–0.36 $P<.001$	0.35 $P<.001$	0.36 $P<.001$	0.34 $P<.001$
Hip circumference	0.37 $P<.001$	0.06 $P = .27$	–0.35 $P<.001$	–0.34 $P<.001$	0.28 $P<.001$	0.34 $P<.001$	0.28 $P<.001$
Waist-to-hip ratio	0.30 $P<.001$	–0.07 $P = .25$	–0.22 $P<.001$	–0.22 $P<.001$	0.30 $P<.001$	0.22 $P<.001$	0.30 $P<.001$
Total caloric intake§	0.05 $P = .38$	0.02 $P = .69$	–0.04 $P = .54$	0.04 $P = .54$	0.02 $P = .76$	0.04 $P = .54$	0.02 $P = .74$
Animal fat intake	–0.05 $P = .38$	0.02 $P = .79$	0.03 $P = .56$	0.03 $P = .56$	–0.07 $P = .23$	–0.03 $P = .56$	–0.07 $P = 0.25$
Animal protein intake	–0.02 $P = .76$	–0.03 $P = .56$	0.04 $P = .50$	0.04 $P = .50$	–0.01 $P = .81$	–0.04 $P = .50$	–0.01 $P = .84$
Plant protein intake	0.07 $P = .19$	0.05 $P = .42$	–0.06 $P = .30$	–0.06 $P = .30$	0.04 $P = .51$	0.06 $P = .30$	0.04 $P = .51$
Testosterone	–0.25 $P<.001$	–0.13 $P = .03$	0.27 $P<.001$	0.27 $P<.001$	–0.18 $P = .002$	–0.27 $P<.001$	–0.17 $P = .003$
DHT	–0.21 $P<.001$	–0.17 $P = .005$	0.26 $P<.001$	0.26 $P<.001$	–0.12 $P = .04$	–0.27 $P<.001$	–0.12 $P = .05$
3α-diol G	0.20 $P<.001$	–0.03 $P = .55$	–0.16 $P = .006$	–0.16 $P = .006$	0.16 $P = .005$	0.16 $P = .006$	0.16 $P = .005$
Estradiol	–0.03 $P = .55$	–0.09 $P = .14$	0.05 $P = .40$	0.05 $P = .39$	–0.02 $P = .73$	–0.05 $P = .39$	–0.02 $P = .76$
SHBG	–0.36 $P<.001$	–0.04 $P = .52$	0.33 $P<.001$	0.33 $P<.001$	–0.31 $P<.001$	–0.33 $P<.001$	–0.30 $P<.001$
T/SHBG	0.26 $P<.001$	–0.01 $P = .85$	–0.23 $P<.001$	–0.23 $P<.001$	0.22 $P<.001$	0.23 $P<.001$	0.21 $P<.001$
IGF-I	0.32 $P<.001$	0.04 $P = .45$	–0.29 $P<.001$	–0.29 $P<.001$	0.24 $P<.001$	0.29 $P<.001$	0.24 $P<.001$
IGF-II	0.21 $P<.001$	0.05 $P = .41$	–0.19 $P<.001$	–0.19 $P<.001$	0.16 $P<.001$	0.19 $P<.001$	0.15 $P<.001$
IGFBP1	–0.39 $P<.001$	0.04 $P = .53$	0.30 $P<.001$	0.30 $P<.001$	–0.36 $P<.001$	–0.30 $P<.001$	–0.35 $P<.001$
IGFBP3	0.19 $P<.001$	0.05 $P = .39$	–0.20 $P<.001$	–0.20 $P<.001$	0.15 $P<.001$	0.20 $P<.001$	0.15 $P = .01$

*Correlation coefficients were determined with log-transformed values of the insulin-related indices.

†HOMA = homeostasis model assessment; QUICKI = quantitative insulin sensitivity check index; I_0/G_0 = insulin/glucose; DHT = dihydrotestosterone; 3α-diol G = 5α-androstane-3α, 17β-diol glucuronide; SHBG = sex hormone binding globulin; IGF = insulin-like growth factor; IGFBP = insulin-like growth factor binding protein.

‡HOMA insulin sensitivity = $10\,000/(I_0 \times G_0)$, where I_0 and G_0 are the fasting serum levels of insulin and glucose, respectively. QUICKI insulin sensitivity = 1/(log (fasting insulin μU/mL) + log (fasting glucose mg/dL)). HOMA insulin resistance = fasting insulin (μU/mL) × glucose (mmol/L)/22.5. The HOMA β-cell function [(HOMA-β) = $(20 \times I_0)/(G_0 - 3.5)$] was also assessed as described *(6,7)*. Serum fasting insulin and glucose levels were measured by using commercially available radioimmunoassays according to the manufacturer's recommended protocols.

§Total caloric intake, animal fat intake, animal protein intake, and plant protein intake were determined using information from the 126 dietary items *(1)* and the nutrient data from the Chinese Food Composition Table. Estrogen levels were measured by radioimmunoassay.

Table 2. Odds ratios (ORs)* and 95% confidence intervals (CIs) for risk of prostate cancer in relation to insulin resistance in a population-based, case–control study from Shanghai, China

Tertiles	Case subjects (N = 128)	Control subjects (N = 306)	OR	95% CI	P_{trend}
Glucose, mg/dL					
Mean (SD)	89.6 (36.7)	78.9 (23.3)			
<69	33	92	1.00	(Referent)	
69–80.9	30	101	0.81	(0.46 to 1.44)	
⩾81	65	107	1.68	(1.01 to 2.80)	.001
HOMA insulin sensitivity†					
Mean (SD)	14.8 (11.5)	20.3 (13.5)			
<14.7	74	99	1.00	(Referent)	
14.7–21.0	26	99	0.36	(0.21 to 0.60)	
⩾21.1	26	100	0.35	(0.21 to 0.60)	.001
QUICKI insulin sensitivity†					
Mean (SD)	0.15 (0.02)	0.16 (0.01)			
<0.153	74	99	1.00	(Referent)	
0.154–0.161	26	99	0.36	(0.21 to 0.60)	
⩾0.162	26	100	0.35	(0.21 to 0.60)	.001
I_0/G_0 ratio					
Mean (SD)	0.18 (0.18)	0.11 (0.07)			
<0.08	27	99	1.00	(Referent)	
0.08–0.11	30	99	1.12	(0.62 to 2.03)	
⩾0.12	69	100	2.54	(1.49 to 4.33)	.001
HOMA insulin resistance†					
Mean (SD)	4.56 (7.63)	1.76 (1.91)			
<1.17	26	99	1.00	(Referent)	
1.17–1.66	36	99	1.00	(0.54 to 1.85)	
⩾1.67	74	100	2.78	(1.63 to 4.72)	.001
HOMA β-cell function†					
Mean (SD)	3.90 (3.73)	2.39 (1.42)			
<1.77	27	99	1.00	(Referent)	
1.77–2.54	31	99	1.16	(0.64 to 2.08)	
⩾2.55	68	100	2.50	(1.46 to 4.26)	.001
Tertiles of WHR‡ and HOMA I_0/G_0 ratio					
Low, low	5	36	1.00	(Referent)	
Low, medium	7	36	1.73	(0.49 to 6.09)	
Low, high	9	25	2.65	(0.77 to 9.18)	
Medium, low	11	39	2.26	(0.71 to 7.21)	
Medium, medium	8	31	2.10	(0.62 to 7.16)	
Medium, high	22	27	7.67	(2.50 to 23.5)	
High, low	10	24	3.78	(1.12 to 12.7)	
High, medium	11	32	3.13	(0.96 to 10.20)	
High, high	42	48	8.21	(2.84 to 23.70)	
BMI§ and HOMA I_0/G_0 ratio					
Low, low	13	39	1.00	(Referent)	
Low, medium	11	28	1.16	(0.45 to 2.97)	
Low, high	19	29	1.93	(0.82 to 4.55)	
Medium, low	8	36	0.66	(0.24 to 1.77)	
Medium, medium	8	33	0.72	(0.27 to 1.97)	
Medium, high	23	30	2.22	(0.96 to 5.17)	
High, low	5	24	0.60	(0.19 to 1.92)	
High, medium	7	36	0.57	(0.20 to 1.59)	
High, high	31	40	2.24	(1.01 to 4.96)	

*ORs adjusted for age, total calories, and BMI. SD = standard deviation; HOMA = homeostasis model assessment; QUICKI = quantitative insulin sensitivity check index; I_0/G_0 = insulin/glucose; WHR = waist-to-hip ratio; BMI = body mass index.

†HOMA insulin sensitivity = $10\,000/(I_0 \times G_0)$, where I_0 and G_0 are the fasting serum levels of insulin and glucose, respectively. HOMA insulin resistance = fasting insulin (μU/mL) × glucose (mmol/L)/22.5. QUICKI insulin sensitivity = 1/(log (fasting insulin μU/mL) + log (fasting glucose mg/dL). The HOMA β-cell function [(HOMA-β) = $(20 \times I_0)/(G_0 - 3.5)$], was also assessed as described *(6,7)*. Serum fasting insulin and glucose levels were measured by using commercially available radioimmunoassays according to the manufacturer's recommended protocols.

‡Tertile cut points for WHR are 0.87 and 0.91.

§Adjusted for age and total calories. Tertile cut points for BMI are 20.3 and 22.5.

were explored by using Spearman correlations with the log-transformed values of the insulin-related indices. We used multiple logistic regression to estimate the association between insulin resistance and prostate cancer risk *(12)*. On the basis of tertile distributions for insulin sensitivity and insulin resistance among control subjects, odds ratios (ORs) and 95% confidence intervals (CIs) were estimated and sequentially adjusted for BMI, sex hormone levels, and IGF levels. All statistical analyses were done with SAS software, version 8 (SAS Institute, Cary, NC).

Among the control subjects, insulin sensitivity negatively correlated with BMI, WHR, and with IGF-I, IGF-II, and IGFBP-3 levels but positively correlated with total serum T, DHT, and SHBG levels (Table 1). By contrast, insulin resistance and HOMA β-cell function positively correlated with all anthropometric variables and with free T (measured as T/SHBG), 3α-diol G, IGF-I, and IGF-II levels (Table 1).

Although case and control subjects were similar in age (median = 71), mean levels of insulin sensitivity, insulin resistance, and β-cell function were statistically significantly different between the two groups (Table 2). In case subjects, insulin sensitivity was 23% lower, insulin resistance (HOMA-IR) was 100% higher, and β-cell function was 75% higher than in control subjects. When the standard cutoff level for HOMA-IR was used, 27.8% of the case subjects and 5.4% of the control subjects were insulin resistant.

Relative to men in the lowest tertile, men in the highest tertile of insulin sensitivity had a 65% reduction in risk of prostate cancer (95% CI = 0.21 to 0.60; P_{trend} = .001), and men in the highest tertile of insulin resistance or β-cell function had a more than twofold risk of prostate cancer (OR for insulin resistance = 2.78, 95% CI = 1.63 to 4.72; OR for β-cell function = 2.50, 95% CI = 1.46 to 4.26) (Table 2). When insulin resistance and WHR were examined together, the effect of insulin resistance was apparent at all levels of WHR, with men in the highest tertile of insulin resistance and WHR having the highest risk of prostate cancer (OR = 8.21, 95% CI = 2.84 to 23.70) (Table 2).

In this population-based study, we showed that insulin resistance is associated with a higher risk of prostate cancer among Chinese men and that insulin sensitivity is associated with a reduced risk of prostate cancer among Chinese men. These results corroborate earlier reports *(1,2)* that abdominal obesity and higher levels of serum insulin are associated with an increased risk of prostate cancer. Although our study population is considered lean (average BMI = 21.9), the insulin resistance effect may be extended to populations with a higher prevalence of obesity, such as Western men, because the insulin effect was also evident among men in the highest tertile of WHR (i.e., those with WHR >0.91).

The observed insulin resistance effect provides a plausible biologic explanation for the long-standing observation that "Westernization" is associated with an increased risk of prostate cancer *(13)*. The underlying mechanism of this association is, however, poorly understood. Westernization is associated with increased intake of saturated fat, red meat, refined sugar, and decreased physical activity, all of which can result in obesity (and abdominal obesity), which in turn can contribute to insulin resistance *(14)*. A diet high in fats—in particular, a high intake of saturated, short-chain, and omega-6 fatty acids—has been associated with insulin resistance *(15)*, whereas a diet that includes a high intake of medium- and long-chain and omega-3 fatty acids has been associated with insulin sensitivity *(15)*.

Insulin resistance may alter the risk of prostate cancer through several biologic pathways, including the obesity–sex hormone pathway *(1)*. Abdominal obesity, especially visceral fat, is associated with increased hepatic glucose production and reduced glucose metabolism, higher levels of free fatty acids, and lower levels of SHBG (thereby yielding higher levels of unbound testosterone) *(16)*. However, our observation that insulin resistance is associated with an increased risk of prostate cancer among men in the lowest WHR group suggests that insulin resistance may also act through non-obesity-related pathways to affect prostate cancer risk. Such pathways may involve changes in inflammation, oxidative stress, and apoptosis, each of which has been associated with insulin resistance *(17–19)*.

The etiology of prostate cancer is likely to involve an intricate interplay of genetic and environmental factors. Whether increased insulin resistance, either through lifestyle changes or genetic susceptibility, increases the risk of prostate cancer warrants further investigation, especially in prospective studies.

REFERENCES

(1) Hsing AW, Deng J, Sesterhenn IA, Mostofi FK, Stanczyk FZ, Benichou J, et al. Body size and prostate cancer: a population-based case-control study in China. Cancer Epidemiol Biomarkers Prev 2000;9:1335–41.

(2) Hsing AW, Chua S Jr, Gao YT, Gentzschein E, Chang L, Deng J, et al. Prostate cancer risk and serum levels of insulin and leptin: a population-based study. J Natl Cancer Inst 2001;93:783–9.

(3) Hsing AW, Gao YT, Wu G, Wang X, Deng J, Chen YL, et al. Polymorphic CAG and GGN repeat lengths in the androgen receptor gene and prostate cancer risk: a population-based case-control study in China. Cancer Res 2000;60:5111–6.

(4) Hsing AW, Chen C, Chokkalingam AP, Gao YT, Dightman DA, Nguyen HT, et al. Polymorphic markers in the SRD5A2 gene and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2001;10:1077–82.

(5) Hsing AW, Chokkalingam AP, Gao YT, Wu G, Wang X, Deng J, et al. Polymorphic CAG/CAA repeat length in the AIB1/SRC-3 gene and prostate cancer risk: a population-based case-control study. Cancer Epidemiol Biomarkers Prev 2002;11:337–41.

(6) Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.

(7) Quon MJ. QUICKI is a useful and accurate index of insulin sensitivity. J Clin Endocrinol Metab 2002;87:949–50.

(8) Goebelsman U, Arce JJ, Thomeycroft IH, Mishell DR Jr. Serum testosterone concentration in women throughout the menstrual cycle and following HCG administration. Am J Obstet Gynecol 1974;119:445–52.

(9) Hanson RL, Pratley RE, Bogardus C, Narayan KM, Roumain JM, Imperatore G, et al. Evaluation of simple indices of insulin sensitivity and insulin secretion for use in epidemiologic studies. Am J Epidemiol 2000;151:190–8.

(10) Perez-Martin A, Raynaud E, Hentgen C, Bringer J, Mercier J, Brun JF. Simplified measurement of insulin sensitivity with the minimal model procedure in type 2 diabetic patients without measurement of insulinemia. Horm Metab Res 2002;34:102–6.

(11) Wallace TM, Matthews DR. The assessment of insulin resistance in man. Diabet Med 2002;19:527–34.

(12) Breslow NE, Day NE. Statistical methods in cancer research. Volume I–The analysis of case-control studies. IARC Sci Publ 1980;(32):5–338.

(13) Hsing AW, Devesa SS. Trends and patterns in prostate cancer risk: what do they suggest? Epidemiol Rev 2001;23:3–12.

(14) Bonora E. Relationship between regional fat distribution and insulin resistance. Int J Obes Relat Metab Disord 2000;24 Suppl 2:S32–5.

(15) Lovejoy JC. Dietary fatty acids and insulin resistance. Curr Atheroscler Rep 1999;1:215–20.

(16) Garaulet M, Perex-Llamas F, Fuente T, Zamora S, Tebar FJ. Anthropometric, computed tomography and fat cell data in an obese population: relationship with insulin, leptin, tumor necrosis factor-alpha, sex hormone-binding globulin and sex hormones. Eur J Endocrinol 2000;143:657–66.

(17) Grimble RF. Inflammatory status and insulin resistance. Curr Opin Clin Nutr Metab Care 2002;5:551–9.
(18) Le Roith D, Zick Y. Recent advances in our understanding of insulin action and insulin resistance. Diabetes Care 2001;24:588–97.
(19) Ceriello A. Oxidative stress and glycemic regulation. Metabolism 2000;49(2 Suppl 1): 27–9.

NOTES

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